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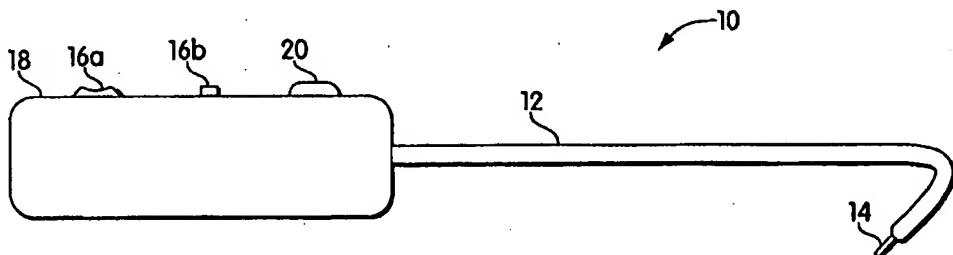
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International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61M 25/01, A61K 9/16, A61M 29/02, A01K 11/00, A61K 9/00, A61N 5/10, F02M 17/04, A61M 25/06, 31/00		A1	(11) International Publication Number: WO 99/30764 (43) International Publication Date: 24 June 1999 (24.06.99)
(21) International Application Number: PCT/US98/26977		(81) Designated States: CA, IN, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(22) International Filing Date: 18 December 1998 (18.12.98)		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(30) Priority Data: 08/993,586 18 December 1997 (18.12.97) US			
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(54) Title: SYSTEMS AND METHODS FOR LOCAL DELIVERY OF AN AGENT



(57) Abstract

A system and method for implanting pellets into myocardial tissue for treatment of coronary artery restenosis, ischemic heart disease, or cardiac conduction disturbances. The mechanism of delivery can be transcatheter via chambers of the heart, endoscopic pericardial approach via minimally invasive transthoracic access, or intraoperative pericardial approach during open-chest surgery. Noncardiac tissues can also be treated.

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SYSTEMS AND METHODS FOR LOCAL DELIVERY OF AN AGENT

5 Field of the Invention

The invention relates to the local delivery of therapeutic agents, and more particularly, to systems and methods that deliver depots of therapeutic agents into a body of tissue to allow for the treatment of a variety of conditions, including coronary conditions and cardiovascular indications.

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Background of the Invention

Disease, injury and surgery can result in localized tissue damage and morbidity. For example, the principal treatment for occlusive vascular diseases is angioplasty, a procedure in which a balloon is inserted into the vessel and then inflated to dilate the area of narrowing. During inflation, the balloon can damage the vessel wall. It appears that as a result of this damage, in 30 to 50% of cases, the initial increase in lumen dimensions is followed by a localized re-narrowing (restenosis) of the vessel over a time of three to six months. Thus, restenosis can result in the dangerous and localized renarrowing of a patient's vessel at the site of the recent angioplasty. Like many other localized diseases, restenosis is complex and at present there is no clinically effective treatment for this disease. Gibbons *et al.*, *Molecular Therapies for Vascular Diseases*, Science vol. 272, pages 617-780 (May 1996).

25 Restenosis, like many other localized injuries and diseases, has responded poorly to pharmacological therapies and agents. Numerous pharmacological agents have been clinically tested, and none have demonstrated an unequivocal reduction in the incidence of restenosis. However, the failure of these pharmacological therapies may arise from the systemic intolerance of the doses required to achieve local beneficial effects or in the difficulty of providing controlled administration of proper dosages over time. Accordingly, one possible reason for the failure of these therapies is that submaximal doses of pharmacological agents are being administered to avoid the serious side-effects that might result from systemic administration of the proper dosage.

To address this problem, various researchers have proposed methods for site-specific delivery of pharmacologic and molecular therapies. These methods include the direct deposition of therapeutic agents into the arterial wall through an intravascular delivery system, systemic administration of therapeutic agents that have a specific affinity for the injured or diseased tissue, and systemic administration of inactive agents followed by local activation.

At present, systems exist that attempt to achieve localized delivery of therapeutic agents. These systems include dual balloon delivery systems that have proximal and distal balloons that are simultaneously inflated to isolate a treatment space within an arterial lumen. A catheter extends between the two balloons and includes a port that can admit within the treatment space between the balloons an aqueous medium, typically one containing a therapeutic agent. Pressure can be applied to the medium to create conditions conducive to intramural infusion. Other balloon-based localized delivery systems include porous balloon systems, hydrogel-coated balloons and porous balloons that have an interior metallic stent. Other systems include locally placed drug-loaded coated metallic stents and drug-filled polymer stents. Wilensky *et al.*, *Methods and Devices for Local Drug Delivery in Coronary and Peripheral Arteries*, Trend Cardiovasc Med, vol. 3 (1993).

Although these systems can provide working devices for local drug delivery, the efficacy of these devices turns on, and is limited by, a number of factors including the rate of fluid flux through the vascular wall, the residence time of the deposited agent and the local conditions and vasculature of the deposition site. Essentially, the success of these systems is limited by the amount of time that a delivered drug will stay resident locally before being carried downstream by circulating blood. Further, to the extent that these systems allow the therapeutic agent to be carried away, these systems run the risk of applying a therapeutic agent to areas of the patient's vasculature where such agents may not be beneficial. Additionally, these existing systems are limited by the amount of drug that can be delivered to the diseased site. Moreover, drug filled polymer stents have structural problems that argue against their use.

It would be advantageous to develop other methods of treatment for patients having localized cardiovascular conditions and in particular to develop methods of treatment that reduce adverse side effects and have heightened efficacy.

Summary of the Invention

It is therefore, an object of the invention to provide methods of treatment of a coronary artery or cardiac indication that provide a longer duration of drug residency at the site of a
5 localized disease.

It is a further object of the invention to provide systems and methods that reduce or eliminate the downstream flow of a locally delivered agent.

10 Other objects of the invention will, in part, be obvious, and, in part, be shown from the following description of the systems and methods shown herein.

To these ends, the invention provides systems and methods for implanting a depot into a tissue wall to thereby deliver a therapeutic agent selected for the condition being treated. In one
15 embodiment, the invention provides systems and methods for delivering a therapeutic agent into the myocardial tissue wall for treating various vascular conditions including restenosis, ischemic tissue, and myocardial infarction. Other applications of the systems and methods described herein include the delivery of angiogenesis compounds that can be implanted into ischemic tissue; and/or antiarrhythmic drugs that can be implanted at the sites of conduction
20 abnormalities. Accordingly, the agent being locally delivered can depend on the application at hand, and the term agent, or therapeutic agent, as employed herein will be understood to encompass any agent capable of being locally delivered including, but not limited to, pharmaceutical compositions or formulations, viral or non-viral vectors (e.g., adenovirus vectors, retroviral vectors and the like), implantable (genetically engineered) cells, plasmid-liposome complexes or other DNA delivery complexes, oligonucleotides or any other suitable
25 composition compatible with the subject being treated.

In one embodiment the invention is understood as apparatus for delivering therapeutic agents, comprising an elongate flexible body having a proximal end and a distal end, a delivery chamber coupled to the distal end of the body and having a space for carrying the therapeutic agent, and a port for releasing the therapeutic agent therefrom. The apparatus further includes an actuator coupled to the distal delivery chamber and being capable of driving therapeutic agent through the port.
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The terms proximal and distal as used herein will be understood to describe opposite ends of a device or element, and generally will be employed so that proximal is understood as "away from the heart" and distal is understood as "towards the heart" or to mean "toward the physician" and "away from the physician" respectively.

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In one embodiment, the apparatus further includes a control mechanism that couples to the actuator and to the proximal end of the body for providing control of the actuator. In this way a user can operate the control mechanism for selectable delivery of the agent. Optionally, the apparatus can also include a "steering" mechanism for bending the distal end of the body to thereby allow the delivery chamber to be selectively aimed or directed within the chambers of the heart. The distal end of the flexible body can be dimensionally adapted to allow for transluminal delivery and for entry into the interior of a patient's heart. This allows the distal end of the apparatus, which carries the delivery chamber, to travel through the patient's vasculature, enter the patient's heart, and butt against or penetrate through the endocardial tissue and penetrate into the myocardium. To this end, the distal end of the delivery chamber can be further provided with a pointed distal end which is adapted to penetrate a tissue wall for delivering the therapeutic agent into the tissue wall.

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In a further embodiment, the apparatus can further include a plunger for driving a therapeutic agent from the delivery chamber. The plunger can include a ratchet assembly for allowing the delivery of discrete volumes of therapeutic agent, or a discreet number of pellets containing a therapeutic agent. Alternatively, the plunger can be provided with a threaded assembly and worm gear assembly for rotatably advancing the plunger into the delivery chamber responsive to a rotating action. Accordingly, an actuator such as a plunger disposed within the delivery chamber can act on pellets of therapeutic agents stored within the delivery chamber to force the pellets from the delivery chamber and implant them within a tissue wall. Optionally a delivery chamber can be dimensioned to receive one or a plurality of pellets containing a therapeutic agent. The activation of the plunger or actuator can be by manipulation of a lever action handle mounted at the proximal end of the flexible body and coupled to the control mechanism. Alternatively, a rotary mechanism, optionally motorized, can be provided for rotating a threaded plunger to advance the plunger within the delivery chamber thereby forcing pellets of therapeutic agent from the chamber.

In a further embodiment of the invention, a mechanism is provided for receiving at least one pellet containing the therapeutic agent and having a pointed shape for facilitating implanting the pellet within a body of tissue. As discussed above, a plunger can be provided for forcing the pointed pellet from the delivery chamber and implanting the pellet within a tissue wall of the patient, such as within the myocardium.

5 In a further aspect, the invention can be understood as pellets adapted for carrying a therapeutic agent into the tissue wall of a patient. In one embodiment, the pellets include a radioopaque marker typically located at the core of the pellet which facilitates the fluoroscopic viewing of the delivery of the pellets.

10 In yet a further aspect, the invention can be understood as methods for providing local delivery of a therapeutic agent which include the step of implanting the therapeutic agent into a portion of myocardial tissue. In one practice, the methods include the step of providing a catheter having a distal end adapted for delivering the therapeutic agent, guiding the catheter into the interior of a patient's heart and disposing the distal end of the catheter against an endocardial wall of the heart for implanting the therapeutic agent into the myocardial tissue. The step of providing a catheter can include the step of providing a steerable catheter which, optionally, can include a drilling element for penetrating a tissue wall such as the endocardium. 15 In one practice, a plurality of pellets containing a therapeutic agent, or a plurality of therapeutic agents, are delivered sequentially into the myocardial tissue. Optionally, each pellet can contain a therapeutic agent and a radio-opaque marker.

20 In one practice of the invention, the local delivery of the therapeutic agent is accomplished by transluminal delivery in which the catheter is steered through access at the femoral artery or vein and directed into the heart. Optionally, a marker can be positioned in a selected portion of a coronary artery to identify a location for receiving the therapeutic agent. In this practice, the marker can be observed fluoroscopically during the procedure, and a treating physician can use the positioned marker for targeting the location of the myocardium 25 into which the therapeutic agent is to be implanted.

In a further practice, the procedure includes a step of endoscopically delivering the therapeutic agent through the epicardium. In yet another practice, the therapeutic agent is implanted into the myocardial tissue during open chest surgery.

5 In a further aspect, the invention provides methods for delivering a therapeutic agent to a septal artery. In one practice, the method comprises the steps of providing a catheter having a distal end that is adapted for delivering the therapeutic agent, guiding the catheter into the interior of a patient's heart and disposing the distal end of the catheter against a septal wall of the heart for implanting the therapeutic agent into the septal tissue.

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Brief Description of the Figures

The foregoing and other objects and advantages of the invention will be appreciated more fully from the following further description thereof, with reference to the accompanying drawings wherein;

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FIG. 1 depicts one embodiment of a catheter having a delivery chamber carried at the distal end;

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FIGS. 2A and 2B depict in more detail the delivery chamber of the catheter depicted in FIG. 1;

FIGS. 3A and 3B depict an alternative delivery chamber for use with the catheter of FIG. 1;

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FIGS. 4A and 4B depict two embodiments of pellets suitable for implantation by the catheter of FIG. 1;

FIG. 5 depicts one method for delivering a therapeutic agent to the myocardium;

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FIG. 6 provides a cross-cut perspective of a coronary artery extending through the myocardium and having pellets of therapeutic agent disposed around the artery; and

FIG. 7 depicts a local drug delivery device having a pistol grip and being suitable for use during an endoscopic procedure.

Detailed Description of the Illustrated Embodiments

5 To provide an overall understanding of the invention, the methods and devices illustrated herein are described with reference to the application of treating cardiac indications by implanting drug delivery pellets into myocardial tissue for the treatment of coronary artery restenosis, ischemic heart disease, cardiac conduction disturbances and other similar conditions. However, it will be understood that the systems and methods described herein are applicable to 10 any condition that can benefit from the implanting of a depot of a therapeutic agent, and the invention is not to be limited to the applications illustrated herein. For example, the techniques herein are directly applicable for implanting therapeutic agents to stimulate angiogenesis.

15 The depot implanting systems illustrated herein include catheter systems for delivery via the chambers of the heart, endoscopic systems for pericardial approach via minimally invasive trans-thoracic access, and systems for use during intraoperative pericardial approach during open-chest surgery. In one practice, the devices deliver a plurality of pellets that surround, or partially surround, an artery being treated. This is understood to achieve the effect of implanting 20 a drug-filled ring around the artery. The pellets remain in the myocardial tissue, and can give off drug(s) for a selected time period and then be absorbed by the body. The systems described herein can implant pellets that contain radio-opaque markers to facilitate viewing the pellets by fluoroscopy during catheter delivery.

25 Fig. 1 depicts one embodiment of a system for providing local delivery of a therapeutic agent. The delivery device 10 includes a catheter 12, a delivery chamber 14, steering switches 16a and 16b, a handle 18, and a delivery control switch 20.

30 The depicted system 10 is a catheter system that can be guided through vascular access at the femoral artery or vein of a patient until the delivery chamber 14 enters into the interior chambers of the patient's heart to implant a depot of drug within the myocardium. To that end, the catheter 12 which extends between the delivery chamber 14 and the handle 18 can be approximately 175 cm to 200 cm in length and can include an elongated rotationally rigid, longitudinally flexible body optionally made of woven polyester fibers, stainless steel wires,

thermoset or thermoplastic polymers or any other material suitable for use as a catheter shaft. The catheter can have a substantially uniform diameter of approximately 0.025 to 0.100 inches (.62 to 2.5 mm).

5 In the embodiment depicted in Fig. 1, the catheter 12 is a steerable catheter that allows or facilitates the guiding of the catheter through the patient's vasculature and into the chamber of the patient's heart. Further, the steerable catheter 12 allows the physician to bend the catheter once the catheter has entered into the interior of the heart, to thereby position the delivery chamber 14 adjacent the area of the endocardial wall through which the delivery chamber is to penetrate. The steering capability of the catheter 12 is illustrated by the bend located at the distal end of the catheter 12. Steering catheters suitable for use with the present invention are known in the art, and include steering catheters employed in Electrophysiology procedures. Electrophysiology catheters typically provide steering through a combination of rotation and tip bending.

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15 One suitable steerable catheter is described in U.S. Patent 5,656,029, which is incorporated herein by reference. This catheter provides an elongate flexible body that carries a bending mechanism at its distal end. The bending mechanism consists of a shape-memory element typically formed of Nitinol which is provided with a memory which makes it assume a straight condition when it is heated, such as by application of an electrical current. The shape memory element extends through the distal portion of the catheter and is adapted to remain straight along its full length in response to a current passing through the element. To control the location of the bending, an electrical bypass is slidably mounted about the bending element. The bypass element can be an elongate cylindrical sleeve formed of a conductive material and through which the bending element can extend. The bypass element can act as a short circuit that bypasses current away from the bending element. Accordingly, the bypass element prevents current from heating the bending element at the location of the bypass. Consequently, the bending element will bend at the location of the bypass. By allowing the bypass to be slid along the length of the bending element, the physician can select the location of the bypass, thereby selecting the location of bending. As the delivery chamber 14 is carried at the distal extremity of the catheter 12, this allows the physician to selectively position the delivery chamber 14 within the interior of the patient's heart.

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The bending elements and bypass elements described above are carried within the catheter 12 and are not shown in Fig. 1, but however are described in detail in the above identified reference. Additionally, it is noted that although the catheter 12 has been described with reference to one type of steerable catheter it will be apparent to one of ordinary skill in the art that other suitable steering mechanisms can be employed with the present invention including steering mechanisms that include actuating poles or wires that extend longitudinally through the catheter body. Moreover, it will be further understood that although the depicted catheter 12 is 5 optionally a steerable catheter, the devices of the invention are not to be limited to steerable devices, and will be understood to encompass conventional catheter systems as well.

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Control of the depicted catheter 12 and the delivery chamber 14 is provided by the integrated hand-held control mechanism and handle 18 mounted on the proximal end of the catheter 12. The control mechanism/handle 18 can be of various types, and the depicted handle 18 is adapted for operating a steerable catheter wherein the bend of the catheter can be 15 selectively controlled by the physician. To these ends, the hand-held control/handle 18 is dimensionally adapted to provide the treating physician with a device that is facile to manipulate and comfortable to hold. Additionally, the hand-held mechanism/handle 18 includes a set of control switches, 16a, 16b and 20 that allow the physician to control the steering of the catheter 12 and the implanting of the depot. Switches 16a and 16b can provide steering control for the 20 catheter 12. The switch 16a can be a slidable switch that allows the physician to control the longitudinal position of the bend within the distal tip of the catheter. The switch 16a can activate the bending mechanism to cause the catheter tip to bend as needed. The control switch 20 can activate the delivery chamber 14 to cause a pellet containing a therapeutic agent to be delivered into a tissue wall.

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It will be apparent to one of ordinary skill in the art that other control mechanisms/handles can be employed with the systems of the invention without departing from the scope thereof. Specifically, other systems can include joystick controls for operating the steerable catheters and can include controls for rotating the angle at which the distal end of the 30 catheter bends. Still other control mechanisms/handles can include pistol grips for providing manual activation of the delivery chamber 14. Other modifications and additions can be made to the control mechanism/handle without departing from the scope of the invention.

Fig. 2A depicts in greater detail one delivery chamber 14 which is suitable for being carried at the distal end of the catheter 12 depicted in Fig. 1. The delivery chamber 14 is sized to hold the plurality of minispheres 22, each of which contains a therapeutic agent. The minispheres 22 are carried within an interior chamber 24 which is bound at the proximal end by a plunger 33 and bound at the distal end by a wall formed of a plurality of flexible finger elements 36 that define a port 30. In the embodiment depicted in Fig. 2A, an optional detent 34 is connected to a sidewall of the chamber 24 to provide a mechanical stop that prevents the minispheres 22 from freely exiting through the port 30. Upon application of mechanical force by the plunger 33, the minispheres 22 can be pushed over the detent 34, for allowing one minisphere 22 to be ejected through port 30.

More specifically, the plunger 33 depicted in Fig. 2A includes a plate 38 and an actuating rod 40. The plate 38 is dimensioned to fill substantially the diameter of interior chamber 24 to provide thereby a surface that is adapted for forcing the minispheres 22 through the chamber 24 and out of port 30. The actuating rod 40 is connected to the plate 38 and provides a mechanical force to plate 38 to advance, or drive, the plate 38 distally into the chamber 24. In one embodiment, the actuating rod 40 extends through the catheter 12 and couples to the control mechanism/handle 18 at the proximal end of device 10. In this embodiment, the control mechanism/handle 18 includes a mechanism that drives the actuating rod 40 distally causing minispheres 22 to be delivered through port 30. Optionally, this embodiment can include a control mechanism/handle 18 that incorporates a ratchet assembly that drives the actuating rod 40 distally in discreet steps wherein a predetermined number of steps corresponds substantially to the diameter of one of the minispheres 22. For example, the depicted control switch 20 can be a rotatable switch that allows for manual actuation of a ratchet assembly contained within the control mechanism/handle 18. The ratchet assembly allows the physician to drive the plunger 33 distally into the chamber 24 thereby driving the minisphere 22 out of the port 30. In this way, the device 10 can allow for the discreet and sequential delivery of minispheres 22 from the delivery chamber 14.

In an alternative embodiment of the invention, the plunger 33 is threaded to mate with a threaded interior portion of chamber 24. Manual or motor-driven rotation of actuating rod 40 will advance or retract the plunger with a finer degree of control than that provided by strictly

linear actuation. Such control over the travel distance of the plunger 33 into and out of the interior chamber 24, gives control over the number of minispheres 22 delivered through port 30.

FIG. 2B provides a head-on perspective of the delivery chamber 14, showing the distal 5 most portion of the delivery chamber 14 as viewed from a position along the longitudinal axis of the delivery chamber 14. Together, FIGS. 2A and 2B show that the distal end of the delivery chamber 14 includes a port 30 that is formed from the convergence of a plurality of flexible arched fingers 36, each of which is formed from a resilient material and each of which is biased to hold the minispheres 22 within the interior chamber 24. Upon action of the plunger 33 to 10 move the minispheres 22 distally, the fingers 36 will yield to the axial pressure and release a minisphere 22. Additionally, in the embodiment depicted in FIG. 2A the optional detent 34 provides further resistance that prevents minispheres 22 from exiting chamber 24 through the port 30 and for providing a tactile sensation that indicates when a minisphere 22 has been released, or has become available to be released, through port 30.

15 The delivery chamber 14 is adapted to facilitate the implantation of a depot of drug within a tissue wall. For example the delivery chamber 14 can be sized and made of a material rigid enough to facilitate the penetration of the delivery chamber within a tissue wall. Accordingly, the depicted delivery chamber 14 can be about 0.010 to 0.050 inches in diameter, 20 and about .05 to .075 inches in length, to have a needle-like profile that is suitable for penetrating tissue. Additionally, the depicted delivery chamber 14 can be formed of stainless steel or of plastic material that is sufficiently rigid to allow the delivery chamber 14 to pass into a tissue wall.

25 FIGS. 3A and 3B depict an alternative embodiment of a delivery chamber suitable for use with the catheter system 10 shown in FIG. 1. The depicted delivery chamber 50 includes a cylindrical sidewall 58 that defines an interior space that houses a plunger 52. The plunger 52 includes a grooved plate 62 that can be rotatably driven along the threads 64 that extend along a portion of the sidewall 58. Accordingly, in this embodiment, the plunger 52 advances into the 30 delivery chamber 50 as the plate 62 turns across, and travels over the threads 64. The distal end of the plunger 52 butts against a stack of nested drug delivery pellets 60 and forces the pellets 60 against the elongate flexible finger elements 54 that, as shown by FIG. 3B, define the port 56.

The delivery chamber 50 implants drug pellets having a hollow, conical shape which facilitates the penetration of the implants 60 into the tissue wall. As shown, the plunger 52 can drive the pellets 60 through the port 56 and into the tissue wall. As discussed above, the flexible fingers 54 are biased to hold the pellets 60 within the chamber 50, however, the mechanical force applied by the plunger 52 will be sufficient to overcome the bias force of the fingers 54. Again as discussed above, a ratchet assembly, a rotary actuator, and/or optionally a detent, can be employed to help the physician control the number of pellets being delivered into the tissue wall. Specifically, the ratchet assembly or rotary actuator controls the distance the plunger 52 is driven into the chamber 50 and the detent provides a tactile sensation each time a pellet 60 is moved a predetermined distance.

The delivery chamber 50 provides an alternative embodiment that allows for the implantation of larger pellets of drugs where the size of the pellet may require a delivery chamber that is too large to readily penetrate through a tissue wall. Accordingly, delivery chambers can be selectively developed for the implantation systems described herein based on the applications of interest and the size of the pellet being delivered. For example, in systems that implant microspheres of drugs having diameters of about 5-15 μm , the delivery chamber can be adapted to hold the microspheres in a fluid medium and a plunger assembly, or other suitable system, can be employed to flush the microspheres from the delivery chamber and into the tissue wall. In this case, the delivery chamber can be simply a hypodermic needle, and a syringe connected to the proximal end of the system can inject the fluid medium through a lumen in the catheter 12. Other delivery chambers can be employed with the systems described herein without departing from the scope hereof.

The systems described above are capable of implanting pellets that contain a therapeutic agent. The therapeutic agent can be any compound that is biologically active and suitable for long term administration to a tissue or organ. The pellets described above can be formed as mini-spheres that are on the order of about 0.005 inches to about 0.040 inches in diameter. Particles of this size are capable of providing a therapeutically effective dose of agent and can remain where implanted, resisting fluid flux through the tissue wall.

Techniques and materials for forming pellets capable of acting as drug delivery implants are well known in the art. In one practice, a solid pellet is formed from a biodegradable polymer

that has been doped or "seeded" with the desired therapeutic agent. Typically, the polymer is a synthetic polymer, such as poly(lactic acid) or polyorthoesters, and is formed by solvent evaporation, spray drying, or phase separation. Such a pellet 70 is depicted in FIG. 4A. The polymer is capable of breaking down over time, allowing the drug to be released into the adjacent tissue. To aid in visualizing the implant by fluoroscopy or x-ray, a sphere of a precious metal, such as gold or platinum, can be covered with the drug-filled polymer 72 in a thickness that provides the desired volume, dosage and/or time release profile. Other acceptable drug delivery implants include the "container" implant which is filled with a liquid drug. A wall of the container is at least partially made of a biodegradable polymer that permits passage of drug molecules at a certain rate. This design is common for injectable microspheres. One advantage is that it can work for drugs that are not amenable to doping in polymers because of heat processes or other incompatibilities. A radio-opaque metal core could be incorporated into this "container" type pellet to facilitate viewing.

Additionally, pellets delivered into or against the tissue wall can be coated with or include adhesive materials that adhere to tissue. Further, coatings can be provided that facilitate the absorption of the pellet into the tissue wall. Such coatings can include fumaric acid, sebacic acid and other similar materials.

FIG. 4B depicts in more detail a pellet 76 suitable for delivery by the delivery chamber 50 depicted in FIGS. 3A and 3B. The pellet 76 is a hollow conical body that provides a pointed end that facilitates delivery of the pellet 76 into a tissue wall. Optionally, the pellet 76 can carry a radio opaque marker (not shown) and, in one embodiment, the radio opaque marker comprises grains of a noble metal which are incorporated into the material of which the pellet 76 is formed.

It will be apparent to one of ordinary skill in the art that other drug delivery implants can be employed with the systems described herein, including disc shaped pills or cylindrical implants that incorporate a solid, drug-filled polymer core with the container-type biodegradable polymer wall. One such implant is described in U.S. patent 5,629,008, which is incorporated herein in its entirety by reference.

FIGS. 5 and 6 depict more explicitly one method according to the invention for implanting a therapeutic agent into a tissue wall. The depicted method is a cardiovascular

treatment for restenosis that can occur in a coronary artery. The method includes the steps of employing an elongate flexible surgical instrument (e.g., a catheter) having a distal end that carries a delivery chamber 14. The distal end is inserted into a vascular system of a patient, such as by insertion via a femoral artery or vein. The delivery chamber 14 is guided through the 5 patient's vascular system until the delivery chamber 14 is disposed within the heart, such as within the left ventricle. Once within the heart, the delivery chamber is employed to implant a therapeutic agent into the tissue of the heart.

In a first step the physician can determine the therapeutic agent, or agents, to be 10 implanted and the depot for the selected agents. The depot may be selected by considering, *inter alia*, the desired time of drug residence within the tissue and the desired dosage to be eluted during the course of the residence. Optionally, the pellets can carry a plurality of therapeutic agents, either by solidifying a plurality of agents within the polymer coating of each pellet, or by providing pellets carrying different therapeutic agents. This latter practice allows 15 the physician to load both active therapeutic agents and agents capable of activating therapeutic agents upon contact, or capable of degrading the polymer wall of an implanted pellet. This can allow for greater time delay before activation of an agent, and for greater selection in the delivery vehicle and the agents and drugs being delivered. Once the agents are selected, the physician can select the delivery chamber to use and can pre-load the delivery chamber with a 20 plurality of pellets, each of which can be a minisphere, a helical, conical pellet, a cylindrical container, or other device capable of being implanted into the myocardium. The physician can preload the delivery chamber 14 with the set of pellets that have been selected to deliver the proper depot of therapeutic agent to the tissue around an artery that is suffering from, or may suffer from, restenosis. Alternatively, pellets containing a desired therapeutic agent can be 25 preloaded into the delivery system, which is provided to the physician as a sterile, disposable item.

Before delivering the preloaded delivery chamber 14 into the heart, the treating physician 30 optionally performs a preliminary step of positioning a radio-opaque marker at the site of restenosis. This allows the treating physician to view the marker during delivery of the pellets. The marker can be a stent, or any viewable marker that will remain present at the site of the localized disease during the implanting of the drug delivery pellets.

In one practice, the marker can be the radio-opaque marker of a balloon being employed during a PTCA procedure. Specifically, as restenosis may arise from the site of the angioplasty, one practice of the invention performs the drug delivery at the same time as the angioplasty. In this procedure, the treating physician leaves the PTCA catheter in place, while the delivery 5 implant system is guided to the target area. A radiopaque marker in the balloon gives fluoroscopic guidance during the implant procedure.

At this time, the physician can guide the implant system along the appropriate delivery route until the catheter enters the interior of the patient's heart. The delivery chamber can 10 approach target areas from within any chamber of the heart. Notably, the practices described herein allow that even septal arteries can be treated for cardiac conditions or to stimulate angiogenesis. In FIG. 5, the delivery chamber is shown as approaching the target area from the interior of the heart, and positioning the delivery chamber against the endocardial tissue over the myocardium. Upon positioning the delivery chamber adjacent the interior tissue wall of the 15 heart, the physician drives the delivery chamber into the tissue and to the targeted area. The physician actuates the control mechanism and ejects a pellet from the delivery chamber, implanting the pellet within the targeted area of the myocardium.

It is a realization of the present invention that the practices described herein are often 20 suitable for arteries normally considered epicardial, with little surrounding myocardial tissue or subepicardial fat in which to implant the drug delivery pellets. Specifically, researchers have noted that tunneled epicardial coronary arteries may represent a normal variant being recognized in up to 86% of vessels. Waller, *Anatomy, Histology, and Pathology of the Major Epicardial Coronary Arteries Relevant to Echocardiographic Imaging Techniques*, Journal of American 25 Society of Echocardiographic Imaging, vol. 2 (1989).

FIG. 6 illustrates a further realization of the present invention. FIG. 6 shows that it is desirable to implant the pellets as close as possible to the artery being treated, and that providing an array of implanted pellets about the periphery of the artery may provide sufficient localized 30 elution of therapeutic agent to prevent restenosis. In one practice, the pellets are implanted through a single point of entry through the myocardium. The physician manipulates the distal tip of the catheter to dispose the port of the delivery chamber at the depicted locations. At each location, a pellet is ejected from the delivery chamber and implanted into the myocardium.

FIG. 7 depicts a further alternative embodiment of the invention. The depicted system 80 includes a short catheter 82 that carries a delivery chamber 84 at its distal end and that connects at its proximal end to a pistol grip control mechanism 88.

5 The system 80 is adapted for use during an endoscopic procedure and to that end the depicted catheter 84 is a short catheter adapted to slide within an endoscopic port that has been placed through the chest and positioned abutting the pericardium. The delivery chamber 84 can be a delivery chamber as discussed above and can be dimensionally adapted to penetrate and extend through the pericardial sac. The delivery chamber can penetrate into the myocardium
10 and thereby allow the physician to implant pellets into the myocardium. Optionally, the catheter 82 can be a steerable catheter which allows the physician to bend the distal tip of the catheter 82 to place the delivery chamber 84 where needed. Alternatively, the catheter can include a deflectable tip, as is known in the art, which the physician can direct to the targeted area. Other modifications to the system 80, including providing the catheter with a fiber optic viewing
15 device to allow the physician to view the interior of the pericardial sac, can be made without departing from the scope of the invention.

20 The depicted pistol grip 88 provides the physician with a manual actuator that allows the physician to control the implanting of pellets within the myocardium. The pistol grip 88 can be a molded plastic assembly of the type well known in the art for actuating a mechanical assembly, such as the plunger assembly of the delivery chamber 14 described above.

25 In a further practice, the techniques of the invention can be employed during an open chest procedure. Specifically, the surgeon performing the open chest operation can employ a delivery device that includes a delivery chamber as described above to implant pellets into the myocardium. Additionally, in this practice, the physician can employ a hypodermic needle to inject a solution containing microspheres of a therapeutic agent. Other practices of the invention can be practiced without departing from the scope thereof.

30 Moreover, the systems and methods for implanting depots of therapeutic agents can be applied to conditions other than those relating to cardiac failure. For example, the systems described herein can be applied to the treatment of muscle tissue afflicted by insufficient circulation. In one practice, the systems described herein are employed to deliver a human

angiogenic growth factor, such as VGEF, which is understood to stimulate the growth of blood vessels. Thus, the systems described herein can promote the survival of muscle tissue that is moribund as a result of poor circulation due to failing or occluding blood vessels.

- 5 Those skilled in the art will know or be able to ascertain using no more than routine experimentation, many equivalents to the embodiments and practices described herein. For example, the devices described herein can be used in cooperation with drilling elements or laser devices capable of forming an opening in a tissue wall, such as the myocardium. The delivery chamber can be inserted into the preformed openings for delivering a therapeutic agent therein.
- 10 Further, pellets according to the invention can include threaded exterior surfaces that facilitate implanting the pellet within a tissue wall. Accordingly, it will be understood that the invention is not to be limited to the embodiments disclosed herein, but is to be understood from the following claims, which are to be interpreted as broadly as allowed under the law.

We claim:

1. A method for providing local delivery of a therapeutic agent, comprising the step of
5 implanting said therapeutic agent into a portion of myocardial tissue.
2. A method according to claim 1, including the steps of
providing a catheter having a distal end adapted for delivering said therapeutic
agent,
10 guiding said catheter into the interior of a patient's heart, and
disposing said distal end against an endocardial wall of the heart for implanting
said therapeutic agent into the myocardial tissue.
3. A method according to claim 1 including the further step of,
15 providing a steerable catheter having a drilling element for penetrating an
endocardial wall.
4. A method according to claim 1, including the step of
delivering a pellet containing said therapeutic agent into the myocardial tissue.
20
5. A method according to claim 4, including the step of
delivering sequentially a plurality of pellets containing said therapeutic agent into
the myocardial tissue.
- 25 6. A method according to claim 1, including the step of
providing a pellet containing said therapeutic agent and a radio-opaque material.
7. A method according to claim 2, including the step of
steering said catheter through the femoral artery and into the heart.
30
8. A method according to claim 2, including the step of
positioning a marker in a selected portion of a coronary artery, for providing a
marker to identify a location for receiving said therapeutic agent.

9. A method according to claim 2, including the step of
penetrating said distal end of said catheter through said endocardial wall, for
delivering said therapeutic agent into said myocardial tissue.
- 5 10. A method according to claim 2, including the step of
delivering through said distal end of said catheter, a pellet having a pointed or
helical, conical end adapted to penetrate said endocardial wall.
- 10 11. A method according to claim 2, including the step of
delivering pellets containing said therapeutic agent and having an outer surface
adapted to adhere said pellets to said endocardial wall.
- 15 12. A method according to claim 1, including the step of
endoscopically delivering said therapeutic agent through the epicardium.
13. A method according to claim 1, including the step of
implanting said therapeutic agent into the myocardial tissue during open-chest
surgery.
- 20 14. A method for delivering a pellet containing a therapeutic agent, comprising the steps of
providing a catheter having a distal end adapted for delivering said pellet,
guiding said catheter through a body lumen and disposing said distal end
proximate a tissue wall, and
delivering said pellet through said distal end with sufficient force to implant said
pellet within said tissue wall.
- 25 15. A method for delivering a therapeutic agent to a septal artery, comprising the steps of
providing a catheter having a distal end adapted for delivering said therapeutic
agent,
guiding said catheter into the interior of a patient's heart, and
disposing said distal end against a septal wall of the heart for implanting said
therapeutic agent into the septal wall.

16. A method according to claim 15, wherein the step of disposing said distal end of the catheter includes a step of,
delivering a pellet containing said therapeutic agent from said distal end with sufficient force to implant said pellet within the septal wall.
- 5
17. A method according to claim 15, wherein the step of disposing said distal end of the catheter includes a step of,
delivering from said distal end of the catheter a pellet containing said therapeutic agent and having a surface adapted to adhere to a tissue wall.
- 10
18. A method for treating vascular restenosis, comprising the steps of
identifying a portion of tissue proximate to a site of a patient's vasculature to be treated for restenosis, and
implanting a therapeutic agent into the portion of tissue.
- 15
19. A pellet, comprising
a therapeutic agent surrounding a radio-opaque material, whereby delivery of the therapeutic agent is facilitated by viewing the position of the radio-opaque material relative to a position of a targeted site for implanting the pellet.
- 20
20. Apparatus for implanting a therapeutic agent within a tissue wall, comprising
an elongate flexible body having a proximal end and a distal end,
a delivery chamber coupled to the distal end of the body and having a space for carrying the therapeutic agent, and a port for releasing the therapeutic agent therefrom, and
an actuator coupled to the delivery chamber and capable of driving the therapeutic agent through the port, whereby the therapeutic agent is implanted within a tissue wall.
- 25
- 30 21. Apparatus according to claim 20, further including
a control mechanism coupled to the actuator and the proximal end of the body for providing control of the actuator, whereby a user can operate the control mechanism for controlling the delivery of the therapeutic agent.

22. Apparatus according to claim 20, further including
a steering mechanism for turning the distal end of the body, to thereby allow the delivery chamber to be selectively guided through a body lumen.
- 5 23. Apparatus according to claim 20, wherein the delivery chamber and the distal end of the flexible body are dimensionally adapted to allow for transluminal delivery and for entry into the interior of a patient's heart.
- 10 24. Apparatus according to claim 20, wherein the delivery chamber includes a substantially cylindrical interior housing dimensionally adapted to store in axial alignment a plurality of minispheres containing a therapeutic agent.
- 15 25. Apparatus according to claim 20, further including
a pointed distal end adapted to penetrate a tissue wall for delivering the therapeutic agent within the tissue wall.
26. Apparatus according to claim 20, wherein the actuator includes
a plunger for driving the therapeutic agent from the delivery chamber.
- 20 27. Apparatus according to claim 20, further including
a ratchet assembly for allowing delivery of discreet volumes of the therapeutic agent.
- 25 28. Apparatus according to claim 20, wherein the actuator includes
a threaded plunger for advancing into the delivery chamber responsive to a rotating action.
29. Apparatus according to claim 20, wherein the delivery chamber is adapted to receive at least one pellet containing the therapeutic agent.
- 30 30. Apparatus according to claim 20, further including
a lever-action handle mounted at the proximal end of the flexible body and coupled to the control mechanism.

31. Apparatus according to claim 20, further including
means for receiving at least one pellet containing the therapeutic agent and
having an arcuate shape for facilitating implanting within a body of tissue.

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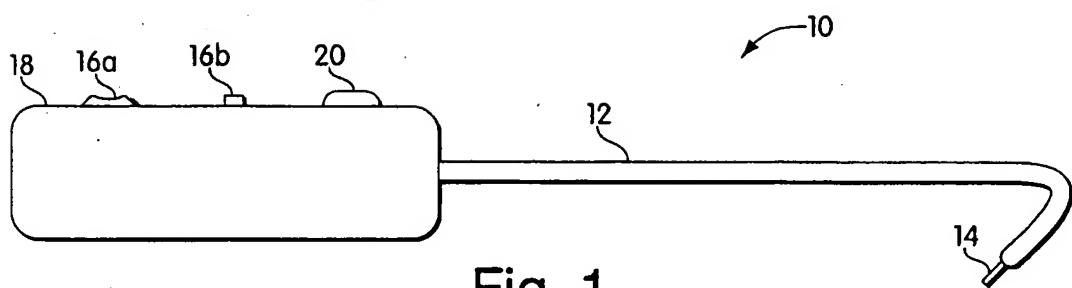


Fig. 1

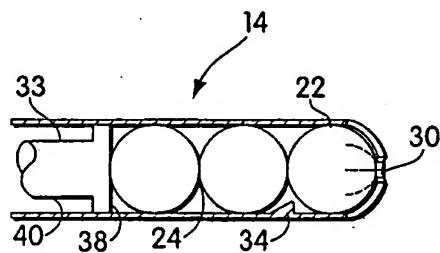


Fig. 2A

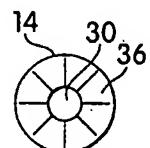


Fig. 2B

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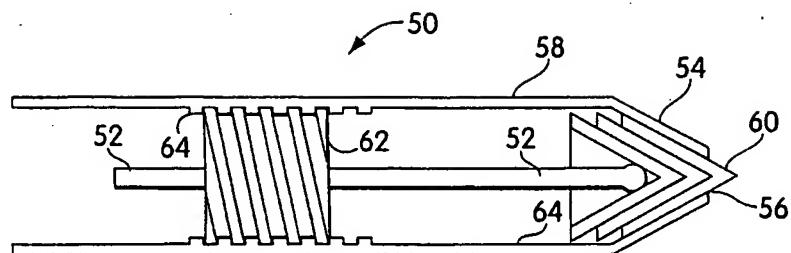


Fig. 3A

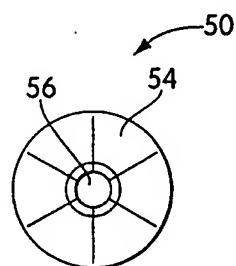


Fig. 3B

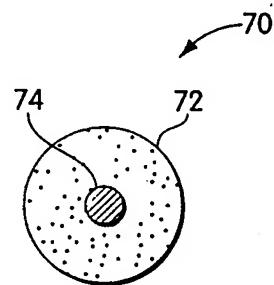


Fig. 4A

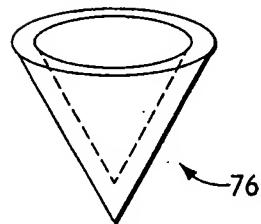


Fig. 4B

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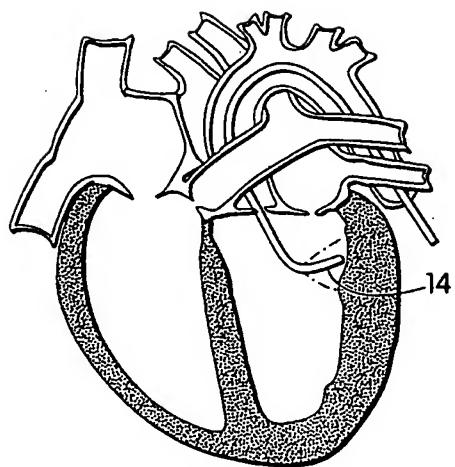


Fig. 5

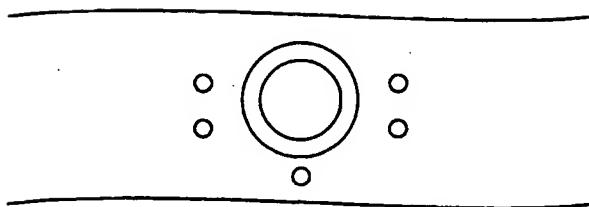


Fig. 6

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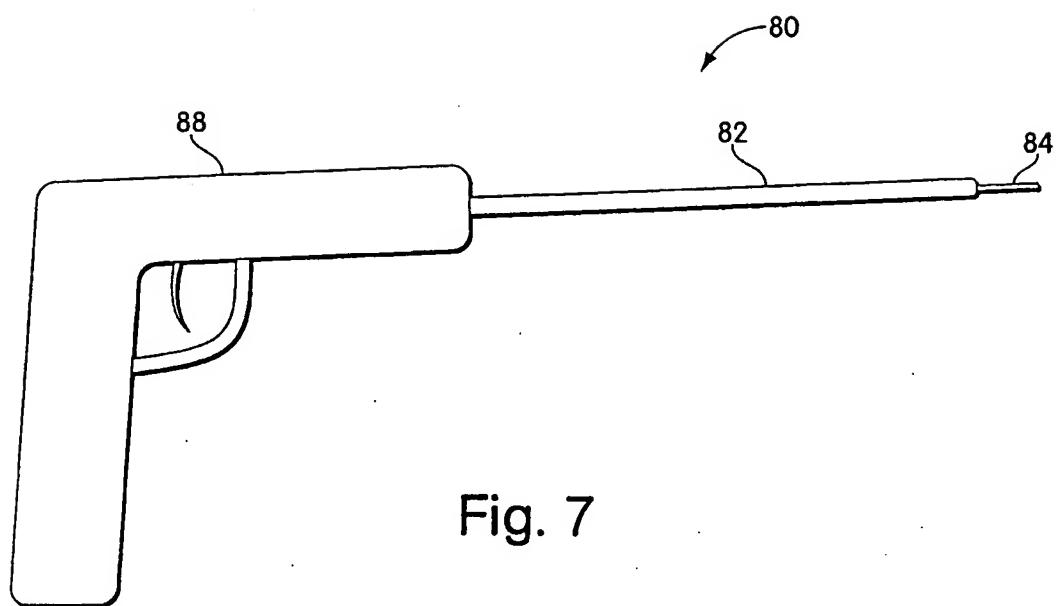


Fig. 7

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 98/26977

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 6	A61M25/01	A61K9/16	A61M29/02	A01K11/00	A61K9/00
	A61N5/10	F02M17/04	A61M25/06	A61M31/00	

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61M A61K A01K A61N F02M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 180 366 A (WOODS W T) 19 January 1993 see column 2, line 64 - column 3, line 30 see column 4, line 22 - column 6, line 23 see figures 1,2,4 --- US 3 991 750 A (VICKERY BRIAN H) 16 November 1976 see column 3, line 58 - column 4, line 7 see column 7, line 29-33 --- US 5 635 215 A (BOSCHETTI EGISTO ET AL) 3 June 1997 see column 3, line 3-30 --- -/-	19,20, 24,29,31 19 19
X		

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "3." document member of the same patent family

Date of the actual completion of the international search

16 April 1999

Date of mailing of the international search report

28.04.99

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INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 98/26977

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 909 250 A (SMITH JOSEPH R) 20 March 1990 see column 2, line 46-53 see column 5, line 11-27; figures 3,4 ---	20,21, 25-27 23
Y	EP 0 584 959 A (SYMBIOSIS CORP) 2 March 1994 see column 2, line 34 - column 3, line 18 see column 4, line 31 - column 5, line 44 see column 9, line 10-16 see figures 1-3 ---	20,21, 25-27,30
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A	US 5 376 071 A (HENDERSON DAVID D) 27 December 1994 see column 6, line 42-46 see figures 5-8 ----	28
A	WO 96 13303 A (NOVOSTE CORP) 9 May 1996 see abstract; figures 2A,2B -----	20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/26977

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 1-18 because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/26977

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